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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,943	03/02/2004	William R. Wilson	8654/2222	2176

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,943	WILSON ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are rejected.

7)☒ Claim(s) *3,4,8,13 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR § 1.114

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 10/20/2006 has been entered.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson, Ph.D. Contact information is provided at the end of this Office Action.

Status of the Claims

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are currently pending and are the subject of this Office Action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 9/3/2001. It is noted, however, that applicant has not filed a certified copy of the GB0121285.1 application as required by 35 U.S.C. § 119(b).

Claim Objections

Claims 3, 4, 8, 13, and 17 are objected to because of the following informalities: the claims recite "the gemcitabine". Gemcitabine is the common name of a chemotherapeutic. As such, the word "the" is not needed before the name gemcitabine. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite DMXAA "or ester thereof". There is insufficient written basis for esters of DMXAA. This is a Written Description rejection.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge

and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

While the specification describes DMXAA at page 1, lines 11-13, it does not describe the structural features or methods of synthesizing any esters of DMXAA. Thus, the disclosure lacks sufficient written description for all species of DMXAA "esters".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siemann *et al.* (prior art of record) in view of Pruijn *et al.* (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546) and van Moorsel *et al.* (Biochemical Pharmacology, 1999, vol. 57, pages 407-415).

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

Siemann *et al.* disclose that DMXAA enhances (*i.e.* potentiates) the efficacy of the chemotherapeutic agents cisplatin and cyclophosphamide in rodent (KHT sarcoma) and human (SKBR3 breast and OW1 ovarian carcinoma) tumor models. DMXAA (17.5 mg/kg) was shown to increase the tumor cell kill of cisplatin and cyclophosphamide by 10-500 fold over that seen with chemotherapy alone (Abstract). The reference thus demonstrates that DMXAA potentiates the antitumor effect of two traditional chemotherapeutic agents in a mammalian tumor model of breast and ovarian tumors. The reference does not disclose combining DMXAA with gemcitabine.

Pruijn *et al.* also disclose enhancing the antitumor activity of an anticancer agent, in this case melphalan, by co-administering melphalan with DMXAA (Abstract). DMXAA is well known in the art as an antitumor agent that inhibits tumor blood flow (page 541, right column, "Introduction"). DMXAA is also disclosed to enhance the antitumor effects of hypoxia-selective cytotoxins (*id.*). DMXAA was formulated in phosphate-buffered saline and melphalan was dissolved in 60% propylene glycol with 40% sodium citrate and both solutions were injected *i.p.* (page 542, left column, "Materials and Methods"). Figure 1 (page 543) demonstrates that DMXAA and melphalan can be administered concomitantly or sequentially and in both cases DMXAA potentiates the effect of melphalan. The reference thus further suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent

caused by falling tumor blood flow (page 545, right column, last full paragraph). The authors conclude that the study demonstrates the potential of DMXAA to "induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions (*id.*). The reference does not suggest combining DMXAA with gemcitabine.

However, van Moorsel *et al.* disclose combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. These antineoplastic agents are known in the art to have clinical activity against various solid tumors (Abstract). Because gemcitabine and etoposide have different mechanisms of action, the drugs were combined and studied in vitro. Gemcitabine has clinical activity in several solid tumors, such as ovarian cancer, NSCLC, head and neck cancer, and pancreatic cancer (page 407). Gemcitabine becomes phosphorylated to its triphosphate and is subsequently incorporated into DNA, followed by one or more deoxynucleotides after which DNA polymerization stops. Etoposide is a widely used anticancer agent that inhibits topoisomerase II (pages 407-408). Gemcitabine was solubilized in PBS for the experiments (page 408). The combined chemotherapy was shown to be synergistic in ovarian and NSCLC cells lines (Table 2). The reference thus suggests combining gemcitabine with other anticancer agents in the treatment of cancer and further demonstrates that such a combination could be synergistic in nature.

In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed methods, compositions, and kits would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. The prior art recognized that DMXAA and gemcitabine have anticancer activity and further

discloses combinations comprising DMXAA and other anticancer agents as well as gemcitabine and other anticancer agents. In both cases, the combined chemotherapy was shown to be synergistic (*i.e.* one drug potentiates the effect of the other). One skilled in the art would have been highly motivated to use other anticancer agents in combination with DMXAA given the disclosures of Siemann *et al.* and Pruijn *et al.* and would have been imbued with at least a reasonable expectation that such a combination would be an effective treatment for solid tumors. Further, the skilled artisan would have had a reasonable expectation that a combination of DMXAA and gemcitabine would be synergistic given their different modes of action.

Moreover, DMXAA and gemcitabine are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural

presumption. Further, it is clear from the prior art that DMXAA potentiates the antitumor effect of a number of anticancer agents (*e.g.* cisplatin, cyclophosphamide and melphalan) because of its mechanism of action (inhibiting tumor blood flow). One skilled in the art would have been imbued with at least a reasonable expectation that DMXAA would also potentiate the effect of the anticancer drug gemcitabine.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

November 7, 2006

Phyllis Spivack 11/8/06

PHYLLIS SPIVACK
PRIMARY EXAMINER